Docket No.: CHROMA 3.0-001 DIV (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Beck et al.

Application No.: 10/371,783

Group Art Unit: 1743

Filed: February 21, 2003

Examiner: Maureen Wallenhorst

For: METHOD FOR PRODUCING PURIFIED HEMATINIC IRON-SACCHARIDIC COMPLEX AND PRODUCT PRODUCED

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Robert A. Beck, do declare as follows:

1. I am a Senior Research Scientist and co-founder of Chromaceutical Advanced Technologies, Inc., assignee of this patent application, a position I have held since the inception of the company. I received a Ph.D. in Analytical Biochemistry in Metabolism from Clark University of Worcester, MA in 1976. In addition to my activities at Chromaceutical Advanced Technologies, I have been teaching in the Department of Chemistry and Food Science at Framingham State College, MA, where I currently hold the position of Professor of Chemistry. Since 1986 I have served as Director of the Framingham Institute for Food Science, Technology and Nutritional Biochemistry, a research arm of Framingham State College. Furthermore, during the period from 1978 through 2000 I was an Affiliate Professor of Biochemistry at Clark University, serving as a research advisor to doctoral candidates. I have authored or co-authored 18 publications, including the textbook, "Food Chemistry and Nutritional Biochemistry" (John Wiley and Sons), a second edition of which is in preparation.

2. I am a co-inventor of the subject patent application. I am familiar with Office Action mailed September 24, 2003. In particular, I am familiar with the observations of

the Examiner regarding the patent reference *Lehmann et al.*, WO 99/07401, English language equivalent U.S. Patent No. 6,372,715 (hereinafter "*Lehmann*") in paragraph 6 of the Office Action, in which it was stated that *Lehmann* teaches that the iron preparation identified in the patent can be present in lyophilized form and that at the time of use the lyophilizate can be reconstituted with a liquid such as a typical pharmaceutical injection media. Therefore, the Examiner concluded in the Office Action that claims 32-34 of the present Application were anticipated in view of this reference.

3. Upon carefully reading *Lehmann*, I have found that it identifies two intravenously administerable iron preparations, "Ferrlecit" and "Ferrum Vitis," for use in the drug combination invention with erythropoietin ("EPO"). Ferrlecit is further described as an iron (III) gluconate complex and Ferrum Vitis as an iron (III) hydroxide saccharate complex. See col. 3, lns. 29-34. Furthermore, *Lehmann* states that the combination drug therapy can be administered in a "fixed combination, i.e. in a single pharmaceutical formulation in which the compounds are present," and that "this can comprise e.g. injection solutions, infusion solutions or lyophilizates, which, for example, are filled into ampoules." It is further stated that "the fixed combination of the active substances in the form of a lyophilizate has the further advantage of simple and safe handling. The lyophilizate is dissolved in the ampoule by the addition of pharmaceutically usual injection media and administered intravenously." See col. 5, lns. 38-51.

4. The two products identified by *Lehmann*, Ferrum Vitis and Ferrlecit, are limited to those that were commercially available in the German medicament market at the time the original German priority patent application was filed, i.e., Aug. 8, 1997. In other words, there is nothing in the patent to suggest that these commercial products were modified in any way, nor that there is any reason to do so. Of the two materials identified, the one that appears to have been used in the single example of the patent, Example 1 at column 11, was "iron sucrose," although the specific product is not identified. Furthermore, the Example states that the iron sucrose was administered in addition to the EPO, not as a fixed combination preparation, and states nothing about the physical form of the iron sucrose other than it was administered by i.v. administration "on the appearance of a functional iron deficiency." Finally, there is no disclosure whatsoever in *Lehmann* of how to lyophilize either Ferrum Vitis or Ferrlecit, nor that the inventors ever did so.

5. In the course of developing the technology on which the subject application is based, I attempted to lyophilize Ferrlecit using the conditions described in detail in the present patent application. I was unable to satisfactorily lyophilize the material in order to

obtain a freeze-dried powder, obtaining instead what can be described as "sludge." I believe that the unsuitable material included moisture that was bound to, e.g., unreacted sugar and/or other by-products and excipients originally present in the Ferrlecit. It was only after Ferrlecit was subjected to the purification process taught in the subject patent application that it could successfully be lyophilized to provide a dried active hematinic product. This is clearly described in the present patent application at paragraph [0076]:

> "In the absence of removing the excipients, particularly hydrophilic excipients, from the AHS (active hematinic species) or iron-saccharidic complex, the AHS is subject to melt-back during the freeze drying process. In other words, the presence of hydrophilic substances results in water being sufficiently bound or retained by the AHS composition in which such hydrophilic substances are present. If higher temperatures are employed to increase the vapor pressure in an effort to remove such bound water, this also can have the undesirable effect of causing the ice phase to melt, thereby impairing freeze drying."

6. In conclusion, it is my opinion that persons skilled in the art, after reading *Lehmann* would have learned that the inventors of the reference had merely employed one of the then existing commercial forms of an intravenously administerable iron preparation, but would not have been informed how to effect freeze drying of such a preparation and, significantly, would not have learned that purification of the commercial preparation was necessary in order to satisfactorily freeze dry it.

I declare under penalty of perjury that the foregoing is true and correct. I further state that I have been warned that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent resulting therefrom. I state that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true.

Dated: March 18, 2004

Robert A. Beck

ROBERT A. BECK

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